less, and a carbomer that will tolerate such high solvent/low water conditions. The amendment is supported in the specification, for example, at page 9, lines 14 to 28, where it is stated that certain of the carbomeric polymers, such as, for example, Carbopol® Ultrez™ 10 and Carbopol® 940, 941, 980 and 981, can be advantageously used to produce gelled compositions, while other carbomers, such as for example, Carbopol® 934P, are not suited to such high solvent/low water conditions.

Added Claim 119 recites a high solvent/low water gelled composition similar to that defined by Claim 36, with the same requirements, for example, of greater than about 50% pharmaceutically acceptable solvent, and about 25% water or less, while avoiding use of the term "solvent-tolerant carbomer." In place of this term, Claim 119 further calls for a carbomer capable of producing a pharmaceutically elegant gel in high solvent/low water conditions. Support for this claim language may be found in the specification, for example, at page 11, line 23 to page 12, line 2. The term "pharmaceutically elegant" is specifically defined at page 11, lines 26 to 27 to mean that the composition is smooth, and not gritty or greasy to the touch.

Rejection Under Section 112

In the Office Action dated April 1, 2002, the rejection of Claim 36 under 35 U.S.C. § 112, second paragraph was maintained. Applicants respectfully disagree with this rejection, and respectfully submit that the term "solvent-tolerant" is not indefinite, for the reasons set forth in the Amendment submitted December 5, 2001. In addition, the Examiner's attention is respectfully directed to the discussion regarding the interaction between polymers, including Carbomers, and solvents, including alcoholic solvents, as set forth in Pena, Chapter 18: "Gel

Dosage Forms: Theory, Formulation, and Processing, Topical Drug Delivery Formulations", Marcel Dekker, pp. 381-388 (1990) ("the Pena reference"). A copy of the Pena reference is enclosed, for the Examiner's convenience. The Pena reference teaches that gelation mechanisms are dependent, *inter alia*, on the interactions between the polymer and the solvent (Pena reference, pp. 381-382). Indeed, the integrity of a gel is based on these interactions (Pena reference, p. 382). Pena further notes that while carbomers are known to form gels, increased amounts of solvent result in decreased interaction between the polymers and solvent, resulting in a change in polymer conformation, which in turn results in reduced gel integrity (Pena reference, p. 385). Increased haziness of the gel also results (id.).

Thus, as would be readily apparent to the ordinarily skilled artisan, the term "solvent-tolerant carbomer" refers to those select carbomers which may be incorporated in gels containing high amounts of solvent, while not suffering from the drawbacks associated with carbomers employed previously.

Nonetheless, in an effort to further define the term "solvent-tolerant carbomer", and in the interest of advancing prosecution of this application, Applicants have amended Claim 36 to clarify that the claimed gels are high solvent/low water compositions comprising greater than about 50% solvent, and about 25%, or less, water. Thus, the term "solvent-tolerant carbomer," when taken in the context of the amended claim (together with the teachings in the specification), would clearly define, to one of ordinary skill in the art, a carbomeric polymer that is suitable for use in such conditions.

In addition, Applicants have added Claim 119, which is similar to Claim 36, but does not contain the "solvent-tolerant" terminology objected to by the Examiner. Instead, Claim 119 specifies that the carbomer used in the gel is one which is capable of producing a

pharmaceutically elegant gel in the high solvent/low water conditions set forth in the claim.

Applicants respectfully submit that the clear meaning and scope of the subject matter defined by these two claims (and thus the claims dependent upon Claim 36), when taken in the context of the application as a whole, are clear and unambiguous. Accordingly, Applicants respectfully request that the rejection under Section 112, second paragraph be withdrawn.

Rejections under 35 U.S.C. § 103(a)

(1) Rejection Over Samour, in view of Pena and Preuilh

Claims 1-19, 21-23, 25-30, 33-36, 38-54, 56-72, 74-87, 90-100, and 102-117 stand rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 5,620,980 to Samour ("Samour"), in view of Pena, U.S. Patent No. 5,225,189("Pena"), and Preuilh et al, U.S. Patent No. 6,106,848 ("Preuilh"). Applicants respectfully traverse this rejection, and submit respectfully that the Office Action still fails to show that the cited art teaches or suggests all of the elements of the claimed embodiments of the invention, as required for a *prima facie* showing of obviousness. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974) (to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art); *see also,* M.P.E.P. § 2143.03. To illustrate this, each of the embodiments defined by independent claims will be addressed separately.

(a) Claims 1 and Claims Dependent Thereon

Claim 1, and all claims dependent thereon (2 to 23, 25 to 30, and 33 to 35), define a composition comprising minoxidil, a thickening agent and a pharmaceutically acceptable solvent, wherein the minoxidil is substantially solubilized in the composition. The thickening

agent is further defined as a *non-carbomeric, organic* thickening agent that *is not hydroxypropyl cellulose*.

Samour describes gels, ointments and creams that comprise minoxidil, in combination with a "penetration enhancer" (see col. 5). The specification makes broad reference to a wide variety of compositions in a table at col. 5, lines 47 to 55, but, as discussed at page 2, lines 14 to 28 of the present application, and as confirmed in the Examples in the present application, there is no enabling disclosure of the vast formulations that may fall within this broad disclosure. The only minoxidil-containing formulations described are the limited number of examples identified in the table at col. 6, line 58 to col. 7, line 25. In this table, only three thickening agents are described: Carbopol 940 (a carbomer), Aerosil R972 (an inorganic silica), and hydroxypropylcellulose. None of these thickening agents meet the requirements of Claim 1.

It must also be noted that none of the formulations in the table bridging columns 6 and 7 contain more than 2% minoxidil. Thus, Samour fails to describe compositions containing higher concentrations of minoxidil, as recited in dependent Claims 4 to 6. As discussed in depth in the instant application, for example at page 2, lines 14 to 28, and comparative Example IV, previous attempts to provide pharmaceutically appropriate thickened formulations containing higher concentrations of minoxidil, particularly on a commercial scale, have failed. Samour contains absolutely no disclosure that would teach one of skill in the art how to overcome these difficulties. Accordingly, Samour also cannot be said to enable compositions containing these higher concentrations of minoxidil.

Combination of Samour with the secondary references fails to overcome these deficiencies. The only thickening agents described in Pena are carbomers, while Claim 1

specifically calls for a *non-carbomeric* agent. Thus, Pena *teaches away* from the invention defined by Claim 1. Additionally, as shown in Example IV in the instant application, Carbopol 934P, the thickening agent described in Pena, fails to produce an acceptable composition containing higher concentrations of minoxidil (*i.e.* 5%).

Preuilh teaches compositions, specifically oil-in-water emulsions, comprising from 0.0001% to 20% by weight of an active ingredient and at least one polymeric emulsifier (column 2, lines 4 to 9; and column 3, lines 43 to 46). A laundry list of exemplary active agents is disclosed in Preuilh at column 3, lines 7 to 42; included among this laundry list are "agents for combating hair loss such as minoxidil" (column 3, lines 41 to 42). In addition, a wide variety of polymeric thickening agents are disclosed in Preuilh, generically and specifically, including the non-carbomeric polymers PEMULEN TR1 and PEMULEN TR2, and the carbomeric polymers CARBOPOL 1342 and CARBOPOL 1382 (column 2, lines 59 to 63).

Applicants submit respectfully that the mere mention in Preuilh of minoxidil as an active ingredient, together with a laundry list of thickening agents, fails completely to disclose or suggest to the skilled artisan the desirability of selecting minoxidil as the active agent and a non-carbomeric polymer as the thickening agent, as defined in Claim 1. The only specific example of a specific formulation in Preuilh fails to even identify a specific active agent (*see* col. 6, line 28), and only indicates a percentage by weight for such unidentified agent of 0.05%. Thus, there is nothing in Preuilh to affirmatively lead one of ordinary skill in the art to modify the compositions described in Samour, as suggested in the Office Action. Moreover, Preuilh teaches only the preparation of oil-in-water emulsions, not *gels*, as exemplified by Samour and Pena. Thus, one of ordinary skill in the art would have no

motivation to combine Samour with Preuilh, or to reasonably expect that such combination might succeed. It goes without saying, of course, that the skilled artisan would have no motivation to combine Preuilh with the other references to come up with *gels*, as defined, *inter alia*, by Claim 2 of the instant application.

(b) Claim 36 and Claims Dependent Thereon

This same combination of references has also been cited against independent Claim 36 (and dependent Claims 38 to 54 and 56 to 61) (and would, presumably, also be applied to newly added Claim 119, since this claim is directed to similar subject matter). Applicants also respectfully traverse this rejection.

As discussed above, Claim 36 is directed to *gelled compositions* that comprise a solvent-tolerant carbomer. The only carbomer taught by Samour or Pena is Carbopol 934P. As specifically taught in the instant application, Carbopol 934P is **NOT** a solvent-tolerant carbomer, and is not suitable for embodiments of the present invention characterized as being high solvent/low water compositions (*see* page 9, lines 26 to 29). Although Preuilh contains a laundry list of potential thickening agents, including carbomers (*see* col. 5, lines 55 to 58), there is absolutely no suggestion to use a *solvent-tolerant* polymer, as recited in Claim 36. Moreover, Preuilh is directed solely to *non-gelled* compositions, and thus *teaches away* from the claimed gels. Accordingly, one of skill in the art would have no motivation to combine Preuilh with Samour and Pena, nor any evidence of a reasonable expectation that such a combination would succeed.

(c) Claim 62 and Claims Dependent Thereon

The combination of Samour, Pena and Preuilh has also been cited against independent Claim 62, and dependent Claims 63 to 72 and 74 to 78. Applicants also respectfully traverse this rejection.

Claim 62 is directed to a composition comprising, *inter alia*, from *greater than 3 to about 8%* minoxidil, and a *non-carbomeric polymer other than hydroxypropylcellulose.* The only non-carbomeric polymer taught by Samour is hydroxypropylcelluose. Pena teaches only carbomeric polymers. Preuilh teaches a laundry list of possible thickening agents, but the only specific formulation taught in Preuilh fails to even identify the active ingredient, much less suggest minoxidil (*see* col. 6, line 28). Moreover, this specific formulation contains only 0.05% active ingredient. Thus, there is nothing in Preuilh that would lead one to prepare the claimed compositions which contain from greater than 3 to about 8% minoxidil. Additionally, as discussed above, Preuilh teaches only the preparation of oil-in-water emulsions, not *gels*, as exemplified by Samour and Pena. Thus, one of ordinary skill in the art would have no motivation to combine Samour with Preuilh, or to reasonably expect that such combination might succeed.

(d) Claim 79 and Claims Dependent Thereon

Independent Claim 79, and dependent Claims 80 to 87, 90 to 100, and 102 to 104, have also been rejected over Samour, in view of Pena and Prieulh. Claim 79 is directed to a *non-gelled* minoxidil composition *consisting essentially of* minoxidil, a thickening agent, and a pharmaceutically acceptable solvent, wherein said composition is *not in the form of an oil-in-water emulsion.*

Samour is directed solely to compositions that contain minoxidil in combination with a penetration enhancing agent (*see* Abstract). Claim 79, and the claims dependent therefrom define over the compositions described in Samour by virtue of the term *consisting essentially of*, if for no other reason. Contrary to the express language of Claim 79, Pena is directed specifically to *gelled* minoxidil preparations (*see, e.g.* Title and Abstract), and Prieulh is directed specifically to *oil-in-water emulsions.* Thus, Claim 79, and *a fortiori*, the claims dependent therefrom, clearly define over all of the cited references. The Office Action fails to provide any rationale for combining these references to arrive at the embodiment defined by this group of claims.

(e) Claims 105 to 109

Claims 105 to 109 also stand rejected over the combination of Samour, Pena and Preuilh. These claims are all directed to processes for preparing minoxidil compositions, comprising specific, active steps. It is stated in the Office Action that Pena teaches the required steps. However, as discussed above, Pena is directed to methods for preparing gels that contain a carbomeric thickening agent. It has not been explained in the Office Action how the claimed method may be taught by the combination of references. Applicants respectfully submit that the claimed processes are patentably distinct from the processes taught in Pena, since the composition being produced by the processes is distinct from that taught by Pena. Moreover, none of the other cited references teach or suggest the preparation of the composition defined in the claims, so it is unclear to Applicants how the instant process could be deemed obvious over such references.

(f) Claims 111 to 118

Claims 111 to 118, which are directed to methods that comprise topically administering the compositions of Claims 1, 36, 62, and 79 to a region of hair loss on a patient, also stand rejected over the combination of Samour, Pena and Prueilh. Applicants respectfully submit that since the compositions defined by the underlying claims patentably define over the cited references, for the reasons discussed above, it follows *a fortiori*, that these method claims are also patentably distinct.

As the discussion above makes clear, although each of the three references relied upon in making the rejection may disclose certain elements of each of the claimed embodiments, there is no teaching or suggestion to combine these elements to prepare the specific compositions defined by Applicants' claims. In fact, in many instances, as mentioned above, the references, when taken as a whole, *teach away* from preparing the claimed compositions. Thus, the rejection relies on selecting and combining elements using hindsight reasoning, using a rationale that comes from the application itself, not from any motivation taught by the prior art. As the CAFC has repeatedly held, such rejections are improper. *See, e.g., In re Kotzab, 217 F.3d 1365, 1371, 55 U.S.P.Q.2D (BNA) 1313, 1317 (Fed. Cir. 2000)* ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed").

For the foregoing reasons, Applicants respectfully submit that the references cited in the Office Action, in any proper combination, fail to establish the *prima facie* obviousness of the claimed invention. Accordingly, Applicants respectfully request that the rejection be withdrawn.

(2) Rejection over Samour, Pena and Preuilh, in view of Grollier and Mousa

All of the previously pending claims also stand rejected over Samour, Pena and Preuilh, in view of Grollier et al, U.S. Patent No. 5,059,606 ("Grollier") and Mousa, U.S. Patent No. 6,171,604 ("Mousa"). Applicants respectfully traverse this rejection, as well.

The deficiencies of Samour, Pena, and Preuilh, both alone and in any proper combination, are discussed above. Grollier adds nothing to overcome these deficiencies. Specifically, the only thickening agent taught or suggested by Grollier is Carbopol 934, the same thickening agent taught by Pena. As discussed above, Carbopol 934 is a carbomer, and thus does not meet the recitation of a non-carbomer in independent Claims 1, 62 and 105. Carbopol 934 is also not a solvent-tolerant polymer, and thus does not meet the requirement of Claim 36.[1] Additionally, in the only thickened minoxidil preparation exemplified in Grollier (*see* Example 5), the minoxidil is *micronized* (having a particle size below 2 microns), and is thus *not substantially solubilized* in the composition, as required by all of the present claims. Thus, Applicants respectfully assert that Grollier adds nothing to make up for the deficiencies of Samour, Pena and Preuilh.

Mousa is directed to methods and preparations for overcoming problems associated with the local application of honey (*see* Abstract). Aside from the fact that it teaches that the honey preparations may be applied to the scalp, this reference has no relevance whatsoever to the instant application. In fact, Mousa says nothing about compositions that contain minoxidil, and fails to provide even the slightest hint that any thickening agents described therein may be suitable for compositions that contain the drug, in a substantially solubilized form. Accordingly, Applicants respectfully submit that one of skill in the art would have no

motivation to combine this reference with any of the other references cited in the Office Action. Moreover, there is absolutely no suggestion in Mousa that any of the thickening agents described therein may be used to produce satisfactory *minoxidil* formulations, *wherein the minoxidil remains substantially solubilized*, as is the subject of Applicants' claims. Thus, Applicants respectfully submit that extracting isolated elements from Mousa, and combining these elements with isolated elements from the other references, with no suggestion in either Mousa or the other references to do so, again amounts to improper hindsight reasoning, which the Court of Appeals for the Federal Circuit has repeatedly ruled is impermissible. *See, e.g., In re Dembiczak, 175 F.3d 994, 999, 50 U.S.P.Q.2D (BNA) 1614, 1617 (Fed. Cir. 1999)* ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references").

Applicants respectfully assert, therefore, that the combination of Grollier and Mousa, to the extent such a combination may properly be made, with Samour, Pena and Preuilh, fails to teach or suggest the invention defined by Applicants claims. Accordingly, Applicants respectfully request that the Rejection under Section 103 be withdrawn.

(3) Unexpected Results

It is asserted in the Office Action that the specification provides "no solubility data of minoxidil at different percent weights." The application teaches, however, for example at page 2, lines 14 to 24, that minoxidil is poorly soluble, and may precipitate out of solution by the addition of additional ingredients, such as thickening agents, and that the high amounts of

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1 Nor would it be suitable for use in the composition of newly added Claim 119.

solvent required to solubililize higher concentrations of minoxidil may be incompatible with many thickening agents. Evidence of this problem is provided by Example IV, which demonstrates that Carbopol 934P could not be used to prepare a 5% gel of the present invention, wherein the minoxidil is substantially solubilized in the composition.

In contrast to this, the other Examples provide both direct and indirect evidence of the surprising benefits of the compositions of the present invention, by disclosing different combinations of thickening agents and solvents at higher concentrations of minoxidil, wherein the minoxidil remains substantially solubilized. Example I, for instance, describes the preparation of a 5% minoxidil gel formulation of the present invention. A pharmaceutically elegant gel was produced, which was nice in appearance, had a smooth consistency, excellent clarity, and moderate viscosity (page 15, lines 6 to 26). Moreover, there was no precipitation of minoxidil in this example.

Although explicit examples are not provided for higher minoxidil concentrations in the claimed range, the specification is replete with disclosure of compositions containing such higher concentrations, wherein the minoxidil remains solubilized. It goes without saying that if Carbopol 934 precipitated out of solution at 5%, it would also precipitate at higher concentrations. Accordingly, Applicants respectfully submit that the evidence provided in the specification is sufficient to show the unexpected benefit of Applicants' compositions, and to further establish the nonobviousness of the claimed invention.

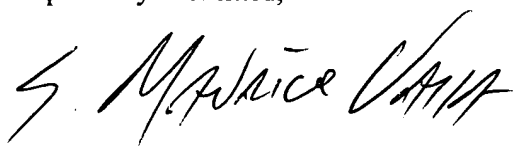
CONCLUSION

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicants respectfully submit that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance of all pending

claims are respectfully requested. If the Examiner remains unpersuaded that the application is in condition for allowance, the favor of a telephone interview with Applicants' undersigned representative is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is entitled **"Version with Markings to Show Changes Made."**

Respectfully submitted,



S. Maurice Valla
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Date: July 31, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 36 has been amended as follows:

36. (Twice amended) A high solvent/low water gelled composition comprising greater than 3% minoxidil, greater than about 50% of a pharmaceutically acceptable solvent, up to about 25% water, and a solvent-tolerant carbomer, wherein said minoxidil is substantially solubilized in said composition.

Claim 110 has been canceled.

Claim 119 has been added.

Topical Drug Delivery Formulations

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18

Gel Dosage Forms: Theory, Formulation, and Processing

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I. THEORY

Gels are transparent to opaque semisolids containing a high ratio of solvent to gelling agent. When dispersed in an appropriate solvent, gelling agents merge or entangle to form a three-dimensional colloidal network structure. This network limits fluid flow by entrapment and immobilization of the solvent molecules. The network structure is also responsible for a gel's resistance to deformation and, therefore, its viscoelastic properties.

A variety of structures are associated with gel networks. Figure 1 illustrates some of the most common ones. *Random coils* are the least ordered and occur most frequently with synthetic polymers such as resins and cellulose derivatives. The *helix* is a more ordered structure formed from the intertwining of two polymer chains. Xanthan gum and starch are typical examples. *Stacks*, or the egg-box model, as it is sometimes called, results from cross-linking of polymer chains by divalent cations. Calcium alginate is a classic example. The *house of cards* structure is characteristic of gel-forming colloidal particles such as bentonite and Veegum. In the case of Veegum, thestructure results from the alignment of the positively charge edges with the negatively charged flat surfaces of the clay particles (1). Because most gels that are used in the pharmaceutical industry are associated with the random coil network, further discussion will be centered around that structure.

Random coil gelation mechanisms are rooted in the polymer–polymer and polymer–solvent interactions. With a given polymer, the gel network forms through successive increases in concentration.

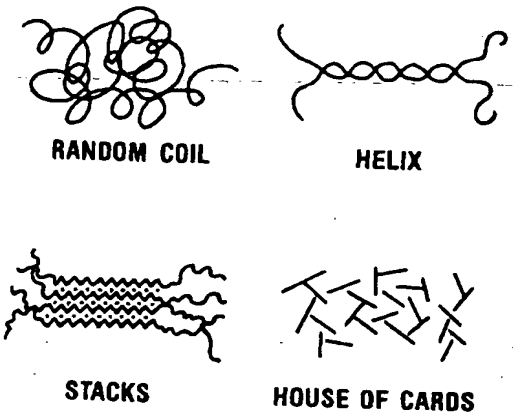

Figure 18.1 Gel structures.

This results in a reduction of the interparticle distances, which subsequently leads to chain entanglement and the development of cross-links. As the number of cross-links increases, the chains lock, solvent mobility is reduced, and a gel forms. Continued polymer addition strengthens the gel network and results in increased resiliency and viscoelasticity.

Although the gel network is basically formed through polymeric interactions, the nature of the polymer–solvent affinity actually determines the integrity of the gel. Classical gel theory distinguishes between three categories of solvents: (1) free solvent that is very mobile; (2) solvent bound as a solvation layer, usually through hydrogen bonding; and (3) solvent entrapped within the network structure. The ratios of the three solvent types in a given gel are dependent on the polymer concentration and the solvent affinity for the polymer. Solvent affinity governs extension of the random coil. The greater the solvent affinity, the more the coil expands and entangles with adjacent coils to form cross-links. In a good solvent, the polymer chains are interpenetrated by solvent molecules, and the solvation layer is enhanced. This facilitates random coil expansion and network formation. In a poor solvent, the polymer chains contract to minimize solvent contact, thereby reducing the effective number of cross-links and weakening the gel network structure.

II. FORMULATION

Gelation theory can be readily applied when formulating gel products. However, before discussing this topic, presentation of some desira-

ble gel characteristics is in ord r. For optimum consumer appeal, the gel should have good optical clarity and sparkle. A high viscosity and a high-yield value are ess ntial, but how high is primarily a matter of intended product application. To preserve product integrity, the gel should maintain its viscosity at all temperatures that may be encountered during shipment and storage. During formulation, there is frequently a trade-off between these optimum characteristics and the chemical requirements of active ingredients.

Carbomer is a commonly used gelling agent that produces gels having a number of these desirable characteristics. The grade, carbomer 934 P NF, is most commonly used in the pharmaceutical industry and has been selected as the exemplary polymer for formulation discussion. Chemically, carbomer 934 P is a cross-linked acrylic acid polymer having a molecular weight of approximately 3×10^6 (2). The gelation mechanism depends on neutralization of the carboxylic acid moiety to form a soluble salt. The polymer is hydrophilic and produces sparkling clear gels when neutralized. Although carbomer tolerates large amounts of alcohol, it does so with decreased viscosity and clarity. Gel viscosity is strongly dependent on pH and the presence of electrolytes. A maximum of approximately 3% electrolyte can be tolerated before precipitation occurs as a rubbery mass. Carbomer gels possess good thermal stability in that gel viscosity and yield value are essentially unaffected by temperature. As a topical product, carbomer gels possess optimum rheological properties. The inherent pseudoplastic flow permits immediate recovery of viscosity when shear is terminated and the high-yield value and quick break make it ideal for dispensing.

The viscosity building effects of carbomer are readily apparent when examining the gelation mechanism in association with the colloidal network structure. As Figure 2 illustrates, before neutralization, carbomer in water exists in its un-ionized form and yields a thin opalescent dispersion of approximately pH 3 (3). At this pH, the polymer is very flexible and behaves like a random coil. Addition of sodium hydroxide or a neutralizing amine to the dispersion shifts the ionic equilibrium in favor of the soluble salt form. This results in ionic repulsion of the carboxylate groups and the polymer becomes stiff and rigid, thereby increasing the viscosity of the water. Overneutralization and excess salts reduce the viscosity of carbomer gels or cause precipitation by the counterion effect.

Figure 3 shows the dramatic effect of pH on the viscosity development of carbomer gels. As pH increases and the carboxylic acid moieties of the polymer are neutralized, viscosity and clarity increase. Acceptable gel clarity and viscosity occur at approximately pH 4.5 to 5.0, but optimum viscosity and clarity are at pH 7. Overneutralization results in a decrease in viscosity that cannot be reversed by addition of acid to lower the pH because an electrolyte is formed.

[redacted]

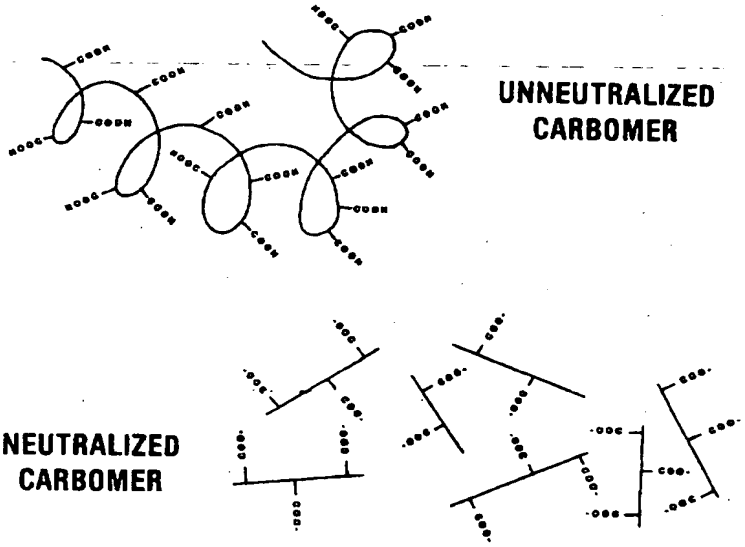

Figure 18.2 Carbomer gel network structures.

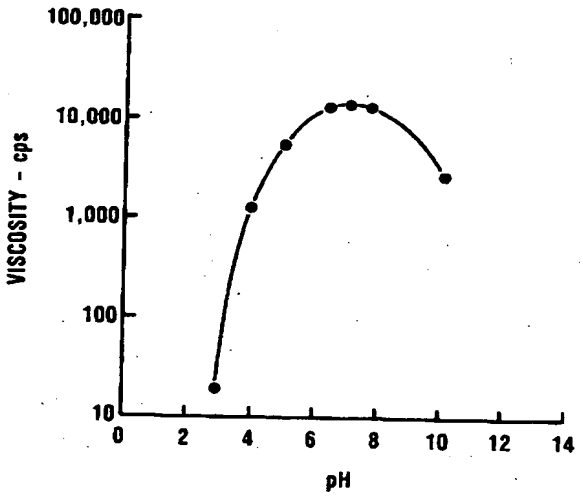

Figure 18.3 pH—viscosity profile of 0.5% (w/w) carbomer 934 P NF in water.

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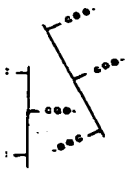
Table 18.1 Alcohol Effects on Carbom r G ls

Carbomer % (w/w)	Alcohol % (w/w)	pH	Viscosity (cP)[a]
0.75	0.0	5.5	12,800
1.25	50.0[b]	5.5	12,800
0.50	20.0[c]	8.2	12,800
0.85	40.0[c]	8.2	12,800

[a]Shear rate 7.61 sec^{-1}.
[b]Isopropanol 70% (v/v).
[c]Alcohol USP, 95% (v/v) ethanol.



Although carbomer can be used to gel formulations with a large proportion of alcohol, the dehydration effects of the alcohol on the polymer are still substantial. As Table 1 indicates, at pH 5.5, the use of 50% isopropanol in a formulation requires 0.5% more carbomer to produce a viscosity equivalent to that of an aqueous gel. At pH 8.2, doubling the concentration of alcohol USP requires 0.35% more carbomer to produce an equivalent gel viscosity. The viscosity responses of the gels to alcohol may be interpreted by its action as a nonsolvent. Because the solvent affinity is reduced, the polymer contracts, with a consequential increase in the interparticle distance and subsequent decrease in the number of entanglements and cross-links. To decrease the interparticle distances and restore the integrity of the gel network structure, a greater concentration of polymer must be used. The reduction in solvent affinity and change in the polymer conformation results in increased haziness of the gel as the alcohol content increases.

The rheograms of carbomer 934 P gels in hydroalcoholic and aqueous formulations are presented in Figure 4 using 0.5% (w/w) and 1.0% (w/w) carbomer, respectively. The characteristic concavity of the rheogram toward the shear rate axis indicates that the gels exhibit pseudoplastic flow. This pseudoplasticity results from a colloidal network structure that aligns itself in the direction of shear, thereby decreasing the viscosity as the shear rate increases. The rheograms also show that the gels exhibit substantial yield values at 666 and 866 dynes/cm^2 for the hydroalcoholic and aqueous formulations, respectively. The yield value is an indication of the extent of formation of a three-dimensional colloidal network structure. The variation in the yield values of the two gels is a reflection of the higher carbomer concentration in the aqueous formulation.

carbomer 934 P NF

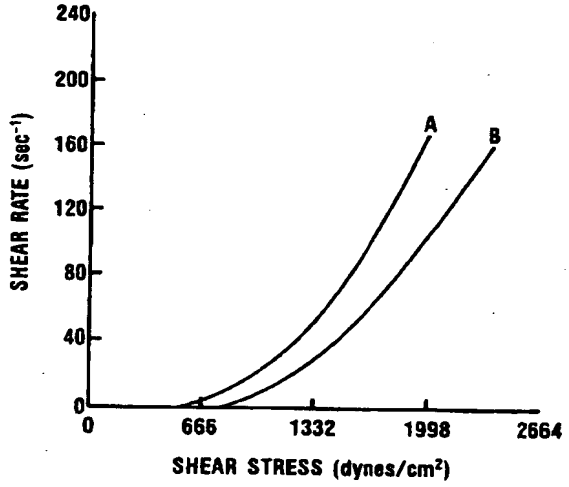


Figure 18.4 Rheograms of carbomer 934 P NF gels. (A) hydroalcoholic gel; (B) aqueous gel.

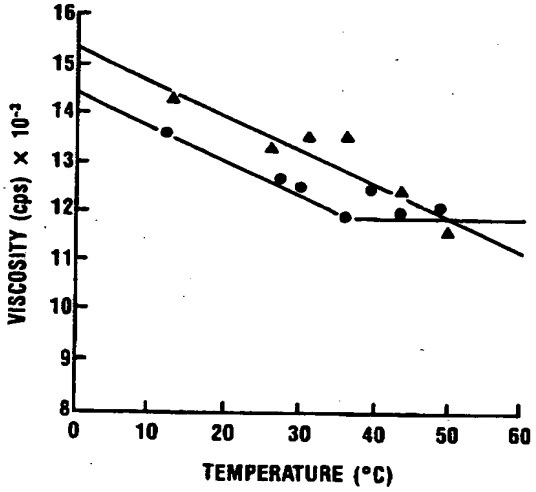


Figure 18.5 Viscosity–temperature plots of carbomer 934 P NF gels: circle, hydroalcoholic gel; triangle, aqueous gel.

Th viscosity—t mperature relationships of the aqueous and hydroalcoholic gels are shown in Figur 5. The hydroalc holic gel shows a plateau at 37°C, whereas the aqueous gel continues to show a general decline in viscosity. As the graphs indicate, the magnitude of the viscosity decline is not substantial over the temperature range covering refrigerated to elevated storage conditions.

III. PROCESSING

To manufacture clear, uniform, air-free gels, certain key processing characteristics must be provided. The nature of carbomer requires initial high-shear mixing to form a uniform smooth dispersion, followed by low-shear planetary mixing during the neutralization—gelling process. Air entrainment during the neutralization process can be minimized by subsurface addition of liquids in conjunction with low-shear mixing. In addition, mixing under vacuum, if available, will withdraw entrapped air from the dispersion during manufacture and prevent further air entrainment by incidental surface breaks. Minimization of air entrainment is necessary from the aesthetic standpoint and, most importantly, from the aspect of controlling fill weights during packaging operations.

gels. (A) hydroal-

A large variety of planetary mixers with and without vacuum capability are available for gel manufacture. The Nauta mixer (4) has a conical mix tank and consists of a lumpbreaker, located at the base of the tank, for high-shear mixing and a rotating auger on a pivot arm for low-shear planetary mixing. The lumpbreaker is flush with the side of the tank and consists of four flat blades spinning at either 1800 rpm or 3600 rpm. The auger can be operated to spiral either upward or downward, depending on whether one desires to deaerate or incorporate materials from the surface into the batch. Both the auger and lumpbreaker are controlled separately. Air entrapment is minimized with the Nauta by mixing under vacuum and by subsurface addition of materials through a port near the base of the mixer.

The Agi-mixer (5) has a hemispherical mix tank. High-shear mixing is provided by the homomixer located at the base of the tank. Counterrotating paddles equipped with scraper blades provide the low-shear planetary mixing action. The homomixer can be operated at only two speeds, whereas the paddles are infinitely variable over the range 0 to 60 rpm. As with the Nauta mixer, aeration can be controlled by mixing under vacuum and by subsurface addition of materials through a basal port.

rbomer 934 P NF gels:
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